Liver Transplantation with Neoadjuvant Chemoradiation is More Effective than Resection for Hilar Cholangiocarcinoma

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Objective: Compare survival after neoadjuvant therapy and liver transplantation with survival after resection for patients with hilar CCA.

Summary Background Data: We developed a protocol combining neoadjuvant radiotherapy, chemosensitization, and orthotopic liver transplantation for patients with operatively confirmed stage I and II hilar CCA in 1993. Since then, patients with unresectable CCA or CCA arising in the setting of PSC have been enrolled in the transplant protocol. Patients with tumors amenable to resection have undergone excision of the extrahepatic duct with lymphadenectomy and liver resection.

Methods: We reviewed our experience between January 1993 and August 2004 and compared patient survival between the treatment groups.

Results: Seventy-one patients entered the transplant treatment protocol and 38 underwent liver transplantation. Fifty-four patients were explored for resection. Twenty-six (48%) underwent resection, and 28 (52%) had unresectable disease. One-, 3-, and 5-year patient survival were 92%, 82%, and 82% after transplantation and 82%, 48%, and 21% after resection ($P = 0.022$). There were fewer recurrences in the transplant patients (13% versus 27%).

Conclusions: Liver transplantation with neoadjuvant chemoradiation achieved better survival with less recurrence than conventional resection and should be considered as an alternative to resection for patients with localized, node-negative hilar CCA.

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Hilar cholangiocarcinoma (CCA) is a devastating disease, and therapy remains a formidable challenge. In 1974, Launois proposed radical resection, including hepatectomy, as a potentially curative operation; initial results demonstrated improved survival.[1] We recently reported our institutional experience with 46 patients, achieving 25% 5-year survival with potentially curative resection.[2] Others have reported similar results, achieving 20–40% 5-year survival for selected patients.[3–10]

Extensive hilar invasion, bilateral liver involvement, and vascular encasement often preclude potentially curative resection. Many patients also have underlying primary sclerosing cholangitis (PSC). CCA arising in the setting of PSC is even more difficult to treat because of either advanced tumor stage or liver disease.[11]

Orthotopic liver transplantation appeared promising because it would obviate problems in achieving tumor-free margins within the liver. Unfortunately, experiences during the late 1980s and early 1990s were poor. The Cincinnati Transplant Tumor Registry reported 28% 5-year survival with a 51% tumor recurrence rate.[12] Eighty-four percent of recurrences were detected during the first 2 years, with 47% occurring in the liver allograft and 30% in the lungs. Incidentally detected tumors fared no better than other tumors, and adjuvant therapy was not associated with survival. The Spanish liver transplant centers reported a similar experience, 30% 3-year survival for 36 patients.[13] A more radical approach with cluster abdominal transplantation reported by the University of Pittsburgh had equally poor results: 20% 3-year survival and a 57% recurrence rate.[14] As a result of these experiences, hilar CCA became a widely recognized contraindication to liver transplantation.[15]

Nevertheless, liver transplantation did achieve long-term survival for a small group of patients with negative margins and absence of regional lymph node metastases.[16] In addition, a small group of patients at our institution treated with primary radiotherapy and chemosensitization alone (without resection) had 22% 5-year survival.[17]

We designed a protocol by combining the benefits of radiotherapy, chemosensitization, liver transplantation, and appropriate patient selection for patients with unresectable hilar CCA in 1993. Preliminary results for 11 patients reported in 2000 were encouraging[18], and in 2004 we reported 82% 5-year survival for 28 patients.[19]

Since 1993 we have continued to treat potentially resectable hilar CCA with resection, including excision of the extrahepatic bile duct, lymphadenectomy, and liver resection. Patients with unresectable tumors and tumors arising in the setting of PSC have undergone neoadjuvant chemoradiation therapy and liver transplantation. We reviewed our experience between January 1993 and August 2004 to compare patient survival after transplantation and neoadjuvant therapy versus resection.

MATERIALS AND METHODS

This study was performed with approval of the Mayo Clinic Rochester Institutional Review Board. Data was abstracted from patient medical records, outside medical records, and from a database maintained on all patients enrolled in our CCA transplant protocol.

Transplant Group

We reviewed data for all patients with hilar CCA treated by surgical resection or the liver transplant protocol at the Mayo Clinic Rochester between January 1993 and August 2004, with follow-up through October 2004.

As previously described,[18–20] we enrolled patients with unresectable CCA or CCA arising in the setting of PSC in the liver transplant treatment protocol. Diagnoses of CCA were established by intraluminal brush cytology, intraluminal biopsy, or a carcinoma antigen (CA) 19.9 level greater than 100 ng/ml in the setting of a radiographic malignant stricture. Since 2003, biliary aneuploidy demonstrated with digital image analysis (DIA)[21] and fluorescent in situ hybridization (FISH)[22] have been considered equivalent to cytology. All patients with de novo CCA were evaluated for resectability by an experienced hepatobiliary surgeon. Clinical staging prior to neoadjuvant therapy included chest and abdomen computed tomography (CT), liver ultrasound, and bone scan. Since 2002, all patients have undergone endoscopic ultrasound with fine needle aspiration of suspicious lymph nodes. Exclusion criteria included previous chemotherapy or radiotherapy, uncontrolled infection, a previous malignancy other than skin or cervical cancer within 5 years, medical conditions precluding transplantation, extrahepatic disease (including regional lymph node involvement), and operative biopsy or attempted resection of the tumor. Between 1993 and 1999, we excluded patients with hilar tumors extending below the cystic duct. Vascular encasement and tumor size were not included in exclusion criteria.

Patients treated in accord with the transplant protocol received neoadjuvant therapy. External beam radiotherapy was administered to a target dose of 4500 cGy in 30 fractions. Concomitantly, intravenous fluorouracil (5-FU) was given at 500 mg/m^2 as a daily bolus for the first 3 days of radiation. Two to 3 weeks after the completion of external beam radiotherapy, a transluminal boost of radiation was delivered using a transcatheter Iridium-192 brachytherapy wire, with a target dose of 2000–3000 cGy. Following brachytherapy, patients initially continued to receive 5-FU at the same dose with an ambulatory infusion pump. During the last 4 years, patients have been treated with oral capecitabine (2000 mg/m^2 per day in 2 divided doses, 2 out of every 3 weeks) as tolerated until transplantation.

All patients underwent a staging operation before transplantation. Between 1993 and 2002, deceased donor liver allocation was largely based on waiting time, and patients underwent operative staging as the time neared for transplantation. Beginning in 2002, following implementation of the Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease liver allocation system, patients underwent operative staging after completion of brachytherapy.

The staging operations were done through a right or bilateral subcostal incision and included a thorough abdominal exploration, with biopsy of any abnormal lymph nodes or nodules, palpation of the hilus to determine inferior extension of tumor, examination of the caudate to assess resectability with caval-sparing hepatectomy, and biopsy of lymph nodes overlying the common hepatic artery at the take-off of the gastroduodenal artery and others along the common bile duct above the duodenum. Extrahepatic metastases, lymph node metastases, and local extension of disease to adjacent organs or tissues precluded liver transplantation.

Only patients with operatively confirmed stage I or II disease underwent liver transplantation. Transplantation was performed with deceased donor livers, living donor right livers, and a familial amyloid domino donor liver. Between 1993 and 1997, transplantation was performed with excision of the vena cava and donor caval interposition using portovenous and venovenous bypass. We adopted caval-sparing hepatectomy in 1997,[23] and this technique was used for CCA patients unless suspected caudate involvement or caudate atrophy was cause for concern regarding the resection margin. Following a hepatic artery thrombosis attributed to radiation injury early in our experience, we have preferentially used a segment of donor iliac artery as an interposition graft to the recipient infrarenal aorta. We avoided the hilus during dissection and divided the bile duct, hepatic artery, and portal vein as low as possible. Since 1999, we have obtained a frozen section examination of the bile duct margin and proceeded with pancreatoduodenectomy if there was involvement. Deceased donor iliac vessels were used for portal vein

and hepatic artery interposition grafts during living donor liver transplantation.

Resection Group

We reviewed medical records for all patients who underwent operative intervention with the intention for potentially curative resection during the same period of time: 1993 through August 2004. As previously reported,[2] our operative procedure included excision of the extrahepatic duct and gall bladder, regional lymphadenectomy, major partial hepatic resection (3 or more anatomic hepatic segments), and biliary reconstruction with Roux-en-Y hepaticojejunostomy. Regional lymphadenectomy included excision of hilar, cystic, pericholedochal, posterior-superior pancreaticoduodenal, portal, and hepatic arterial lymph nodes. Segmental or tangential portal venous resection was performed as necessary to achieve potentially curative resection.

Preoperative studies included endoscopic retrograde cholangiography (ERC) and/or percutaneous transhepatic cholangiography (PTC) to assess the proximal and distal extension of disease. Ultrasonograpy and CT of the chest and abdomen were obtained for evaluation of local and metastatic disease. Visceral angiography was used selectively to define vascular involvement.

All patients had histologic confirmation of biliary adenocarcinoma on resected specimens. No patients received neoadjuvant therapy before resection, and selected patients received adjuvant therapy after resection. Resection was considered potentially curative (R0) if the margins of resection were tumor-free.

Analysis

Continuous variables are reported as the mean ± SD. Comparisons between continuous variables were performed using the Student *t* test. Survival and recurrence rates were calculated using the Kaplan-Meier method. Comparisons of discrete variables in the Kaplan-Meier analyses were made using the log-rank test. *P* values less than 0.05 were considered statistically significant. All analyses were conducted using SAS version 8.2 (SAS Institute Inc, Cary, NC) on a Sun Ultra II computer (Sun Microsystems Inc, Palo Alto, CA).

RESULTS

Seventy-one patients were enrolled in the transplant protocol and 38 (54%) underwent liver transplantation as of August 2004. Fifty-four patients underwent attempted resection, and 26 (48%) had resections with intent to cure. The patients that eventually underwent transplantation were significantly younger and had higher incidences of PSC ($P < 0.001$) and inflammatory bowel disease ($P = 0.03$) than those that underwent resection (Table 1). The predominance of males that underwent transplantation compared with those that underwent resection also approached statistical significance ($P = 0.08$).

TABLE 1. Transplant Recipients and Resection Patients

	Transplant Recipients (n = 38)	Resection Patients (n = 26)	*P*
Age (mean ± SD)	48 ± 10	63 ± 12	<0.001
Gender (M:F)	28:10	14:12	0.08
Primary sclerosing cholangitis (no. [%])	22 (58)	2 (8)	<0.001
Inflammatory bowel disease (no. [%])	11 (31)	2 (8)	0.03

Transplant Group

Seventy-one patients were enrolled in the transplant protocol and received neoadjuvant chemoradiotherapy. Five patients died (4 from sepsis, 1 from a pulmonary embolism) and another 4 patients had evidence for disease progression beyond transplant criteria during or after completion of neoadjuvant therapy, and later died of CCA. Sixty-one patients underwent operative staging, and 14 (23%) had findings precluding subsequent transplantation. These findings included: regional lymph node metastases (8 patients); extensive local disease with invasion of adjacent organs and tissues (3 patients); widespread intrahepatic metastases (2 patients); and isolated peritoneal metastasis (1 patient). As of August 2004, 1 patient was awaiting staging, 9 patients were awaiting liver transplantation, and 38 had undergone transplantation—30 with deceased donor livers, 1 with a familial amyloid domino donor liver, and 7 with living donor right livers.

Pathologic examination did not detect any residual tumor in 16 of the 38 explanted livers. Eight of these patients had unequivocal histologic or cytologic confirmation of tumor before administration of neoadjuvant therapy. Three patients had suspicious cytology, malignant-appearing strictures, and underlying PSC. Two patients had malignant-appearing strictures and high CA 19.9 levels without underlying PSC. Three patients had malignant-appearing strictures with PSC and positive DIA and FISH tests for aneuploidy. Three of 14 patients with positive findings at the staging operation also did not have histologic or cytologic confirmation of tumor prior to administration of neoadjuvant therapy. None of the 38 transplant recipients were found to have extraheptic disease at the time of liver transplantation.

Five patients developed recurrent CCA at 22 months (abdominal carcinomatosis), 22 months (chest wall, percutaneous biliary tube site), 40 months (mediastinum), 54 months (bone), and 64 months (pancreas, possibly residual duct in PSC patient), and died 24, 28, 76, 83, and 67 months, respectively, after transplantation. One-, 3-, and 5-year recur-

rence rates were 0%, 5%, and 12%, respectively, and mean time to recurrence was 40 months.

Three patients died of surgical complications. One patient was the recipient of a marginal deceased donor liver with hepatic artery calcification. The patient died at home 3 months after transplantation, presumably due to late hepatic artery thrombosis. Two patients died of complications following living donor liver transplantation. One died at 2 months because of a leak from a retained segment of a Wall stent that had been inserted before referral for transplantation. The other patient developed a bile leak, late (3 months) hepatic artery thrombosis, and died 4 months after retransplantation with a deceased donor liver.

Five of 22 (23%) patients with PSC had unsuspected tumor involvement of the common bile duct margin. Four underwent pancreatoduodenectomy at the time of liver transplantation. One patient (described above) died of presumed late hepatic artery thrombosis. There was no evidence for tumor recurrence at autopsy. The other 3 patients are alive and disease-free 24 to 72 months after combined pancreatoduodenectomy and liver transplantation. The fifth patient had a suspicious lesion on the gall bladder at the staging operation. Biopsy did not show tumor involvement, but the patient suffered a postoperative gall bladder perforation requiring reoperation with tube cholecystostomy placement. Extensive intraperitoneal adhesions precluded pancreatoduodenectomy at the time of transplantation. Despite microscopic disease at the common bile duct margin and confirmation of gall bladder involvement with examination of the explanted liver, the patient had not yet developed clinical evidence for recurrence 8 months after transplantation. Another patient had undergone partial choledochal cyst excision with choledochoduodenostomy 19 years before developing CCA and underwent en bloc pancreatoduodenohepatectomy during liver transplantation. This patient was alive and disease-free 35 months after transplantation.

Survival for all 71 patients enrolled in the transplant protocol was 79%, 61%, and 58% at 1, 3, and 5 years after enrollment in the protocol, respectively (Fig. 1). Survival for the 61 patients that underwent operative staging was 88%, 70%, and 66% at 1, 3, and 5 years. One-, 3-, and 5-year survival rates were 98%, 86%, and 81% for the 47 patients with negative staging operations compared with 63%, 25%, and 25% for the 14 patients with positive findings. Survival for the 38 patients that underwent liver transplantation was 92%, 82%, and 82% at 1, 3, and 5 years after transplantation (Fig. 2). There was no difference in survival after transplantation between those patients with and without underlying PSC. Survival for the 16 patients without underlying PSC was 94%, 71%, and 71% at 1, 3, and 5 years after transplantation (Fig. 3). Although the 8 patients without histologic or cytologic confirmation of tumor were thought to have had accurate diagnoses, these patients did not have a substantial

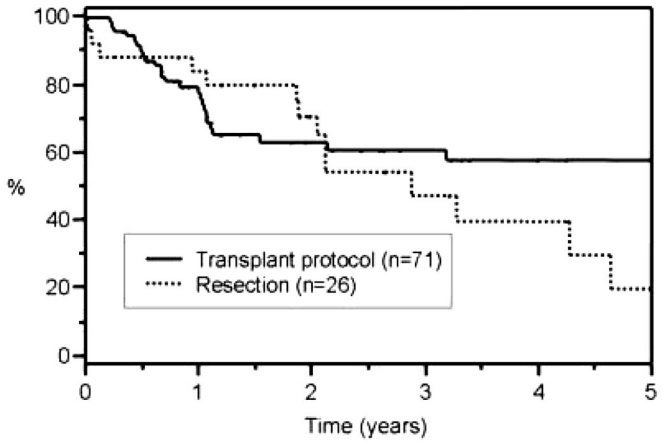

FIGURE 1. Patient survival from start of neoadjuvant therapy (all 71 patients in transplant protocol) or resection.

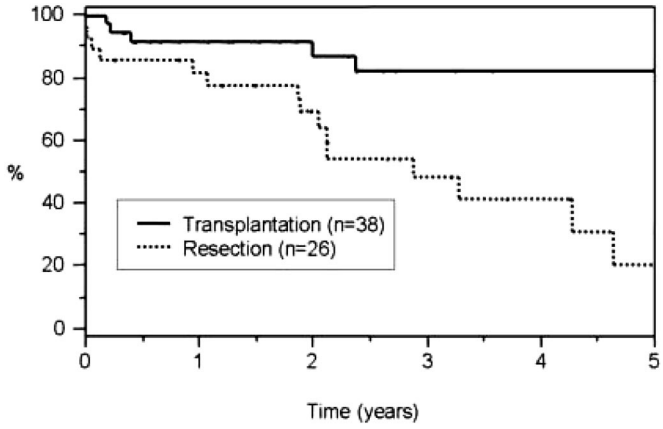

FIGURE 2. Patient survival from operation.

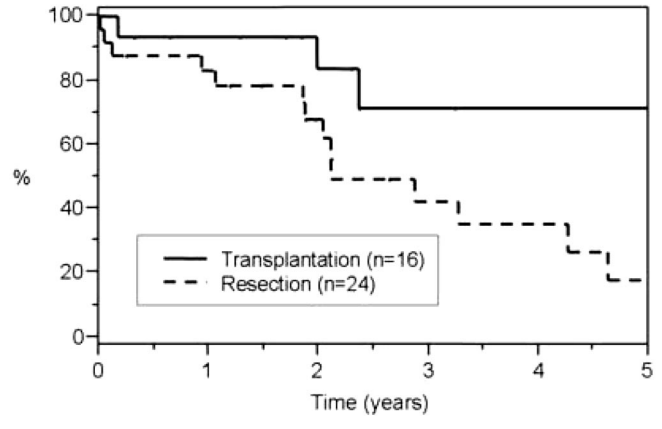

FIGURE 3. Survival after operation for patients without PSC.

impact on survival after transplantation. Five-year survival was 80% with omission of these patients.

Resection Group

Fifty-four patients in the resection group underwent abdominal exploration with the intention of performing a potentially curative resection. Twenty-eight patients (52%) were unresectable because of vascular encasement (11 patients [39%]), distant lymph node metastases (7 patients [25%]), peritoneal metastases (5 patients [18%]), intrahepatic metastases (4 patients [14%]), and inflammatory adhesions precluding safe resection (1 patient [4%]). Twenty-six of the 54 (48%) patients in the resection group underwent resection at the time of operation. Resections were accomplished with right hepatectomy (12 patients [46%]), left hepatectomy (13 patients [50%]), and extended right hepatectomy (1 patient [4%]). Concomitant caudate (segment I) resections were performed for 10 (38%) patients. Twenty-three of the 26 resections (88%) were R0 and 3 (12%) were R1 with microscopic disease involving the hepatic duct margins.

Twenty-five of the 26 resection specimens confirmed invasive carcinoma, including one with mucinous and another with polypoid tumors. One of the 2 patients with underlying PSC had carcinoma in situ. Eight of 26 patients (31%) had regional lymph node involvement, and 1 of these patients had an R1 resection with residual hepatic duct involvement. Fifteen of the patients (58% of the resection group) had both absence of regional lymph node metastases and R0 resections.

Three patients (12%) died within 30 days of resection due to arrhythmia, sepsis from a bile leak, and an unknown cause at home. Recurrent CCA developed in 9 (35%) of the resection patients: 4 in the hilus, 2 in the liver, 1 adjacent to the portal vein, 1 in the peritoneum, and 1 in the umbilical skin (trocar site). The mean time to recurrence was 21 months. One-, 3-, and 5-year recurrence rates were 5%, 44%, and 58% for all 26 patients and 7%, 45%, and 63% for the 15 node-negative R0 resection patients.

Survival for 26 patients who underwent resection was 82%, 48%, and 21% at 1, 3, and 5 years, respectively, with a median survival of 34 months (Fig. 2). The 16 patients with negative nodes and R0 resections had similar 1-, 3-, and 5-year survival at 87%, 53%, and 18% (Fig. 4).

Comparing Resection and Transplantation

Patient survival was significantly higher after liver transplantation than after potentially curative resection ($P = 0.022$). Patient survival was also higher for the entire transplant group (all 71 patients enrolled in the transplant protocol) than for those patients that underwent resection (Fig. 1). There was a lower incidence of tumor recurrences in the transplant patients than the resection patients (13% versus 27%), and recurrences became apparent later after transplantation than after potentially curative resection (mean 40 months versus 21 months).

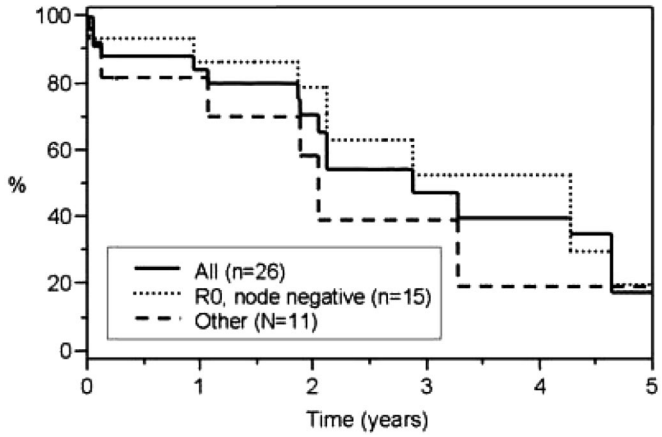

FIGURE 4. Patient survival after resection.

Transplantation also favorably compared with resection when the analysis was limited to patients without underlying PSC (Fig. 3). Twenty-four of 26 patients that underwent potentially curative resection did not have underlying PSC, and their actuarial survival at 1, 3, and 5 years was 83%, 42%, and 18%, respectively. Sixteen of the 38 transplant recipients did not have PSC, and their actuarial survival was 94%, 71%, and 71% ($P = 0.05$). One-, 3-, and 5-year actuarial recurrence rates for the non-PSC patients were 5%, 51%, and 51% after resection compared with 0%, 25%, and 44% for the non-PSC transplant recipients ($P = 0.28$).

DISCUSSION

We designed a protocol combining the known benefits of radiotherapy, chemosensitization, and liver transplantation in 1993 in an attempt to develop an effective therapeutic approach for patients with unresectable hilar CCA. As previously described,[18–20] our protocol was to treat patients with high-dose neoadjuvant radiotherapy and chemosensitization to lesson the likelihood of local recurrence and tumor dissemination at the time of transplantation. Operative staging was intended to limit transplantation to patients with localized disease and absence of regional lymph node metastases.

Since 1993, our institutional approach to the treatment of hilar CCA has been conventional resection for patients with tumors that appear amenable to resection and liver transplantation with neoadjuvant chemoradiotherapy for those with unresectable tumors and tumors arising in the setting of PSC. Herein, we compared our results with the specific aim of assessing relative efficacy of transplantation with neoadjuvant therapy and conventional resection.

Twenty-six of 54 patients that underwent operation with the intention of achieving an R0 resection underwent resection. Five-year survival after resection was 20%. In

comparison, 71 patients received neoadjuvant therapy, and 38 underwent transplantation. Five-year survival after transplantation was 82%, significantly higher than results with resection.

Twenty-six of 54 (48%) patients with tumors that appeared resectable underwent resection at operation, and an R0 resection was achieved for 23 of the patients. A third of the patients eventually developed recurrent disease at a mean of 21 months after resection. Eight of 9 recurrences were located locally/regionally, and 1 was peritoneal carcinomatosis. In contrast, an R0 resection was achieved in 37 of the 38 patients that underwent transplantation. Only 5 of the 38 (13%) patients developed recurrent disease at a mean of 40 months after transplantation. Unlike recurrences after resection, recurrences after transplantation were more likely to be at distant locations.

We acknowledge difficulties in comparing results between the resection and transplant groups. The transplant group was significantly younger and with higher incidences of PSC and inflammatory bowel disease than the resection group. Furthermore, by protocol design, none of the patients that underwent liver transplantation had regional lymph node metastases. Medical selection criteria were more stringent for the transplant group. Tumor selection criteria were less stringent for the transplant group that included patients with vascular encasement, bilateral hepatic duct involvement, and underlying liver disease (PSC). Furthermore, none of the patients in the transplant group were candidates for resection because of either local progression of disease or underlying PSC.

We analyzed subsets of both groups in an attempt to achieve more direct comparisons. Since all of the transplant patients had node-negative disease, we calculated survival for the R0 resection patients with node-negative disease. Somewhat unexpectedly, the 16 node-negative, R0 resection patients fared no better than the resection group as a whole. We compared results with resection to transplantation for patients without underlying PSC, and 5-year survival was again significantly higher for the transplant recipients. We also observed that patient survival for the entire transplant group—58% at 5 years for all 71 patients from initiation of neoadjuvant therapy to last follow-up, including those that died prior to staging or with findings at staging precluding transplantation—exceeded the 20% 5-year survival for those patients that actually underwent resection.

Our results with resection are similar to those reported by other specialized hepatobiliary centers.[3–10,24] Treatment failures were most commonly due to local/regional recurrence.[25] This pattern of recurrence likely reflects the infrequency of truly negative radial and longitudinal resection margins. Interestingly, earlier results with liver transplantation alone were very comparable to those with conventional resection. Most patients succumbed to recurrent disease with less than 30% 5-year survival. With one exception,[26] even incidental CCA discovered in the explants of patients that underwent transplantation for PSC fared just as poorly as known, and presumably more advanced, tumors.[12,13,27]

Our results with transplantation after neoadjuvant therapy differ considerably from reports of liver transplantation alone as primary treatment of CCA. Local/regional recurrences were less common and patient survival greatly exceeded results reported by others after liver transplantation alone. We attribute this difference to the high-dose neoadjuvant radiotherapy with chemosensitization. Few, if any, changes in operative technique during the past 10 to 12 years could remotely account for the decrease in local recurrence that we have observed with our treatment protocol.

Multiple studies have demonstrated potential efficacy of radiotherapy with and without chemosensitization as palliative therapy,[17,28,29] adjuvant therapy,[8,29,30] and neoadjuvant therapy prior to conventional resection.[31] Efficacy, however, is limited by dose-related toxicity, especially hepatotoxicity. Liver transplantation has the obvious advantage of reversing hepatotoxicity and enabling the use of higher dose therapy with an aim to achieve better local control than is possible with resection or transplantation alone.

Explanted livers from transplant recipients demonstrated marked changes as a result of neoadjuvant chemoradiotherapy. Most livers showed hilar inflammation with necrosis in the hilus and extrahepatic duct. Although residual carcinoma was not detected in 16 explanted livers, 9 of these patients had unequivocal histologic or cytologic confirmation of tumor prior to administration of neoadjuvant therapy. This finding attests to the efficacy of neoadjuvant chemoradiotherapy. Although one might be skeptical about the diagnoses of CCA in the other 7 patients, omission of these patients from survival analysis did not have a substantial effect, reducing 5-year survival from 82% to 80%.

Liver transplantation has several advantages over conventional resection in its potential to achieve complete extirpation of tumor. Hepatic duct tumor involvement is difficult to assess before resection and is the most common cause for failure to achieve an R0 resection. This problem is completely avoided by liver transplantation. Liver transplantation facilitates removal of all hilar neural and lymphatic tissue and resection of the caudate. Liver transplantation also obviates the need to preserve arterial and portal venous inflow to the remaining liver. Liver transplantation affords wider excision than what can usually be obtained with resection.

Experiences with resection have clearly demonstrated an improvement in survival with the inclusion of hepatic resection as an essential component of surgical therapy. However, overall survival achieved with resection has remained remarkably static since that adaptation. Additional improvement in survival after resection will likely only come from a more radical operative approach and/or development

of consistently effective adjuvant therapy. Indeed, a benefit of wider excision, including resection of the portal vein, was suggested by Neuhaus et al,[32] who reported 72% 5-year survival for patients that underwent R0 resections with right trisegmentectomy and portal vein resection. As with other experiences, however, few patients (<30%) had tumors amenable to potentially curative resection. Regardless of the resectability rate, if further study of this approach confirms these findings, survival with this approach would move toward that of transplantation with neoadjuvant therapy. Transplantation with neoadjuvant therapy could then be reserved for those patients with unresectable disease.

Twenty-eight of the 54 patients (52%) that underwent operation with the intention to achieve resection were found to have unresectable disease. Reasons for unresectability included distant lymph node metastases, peritoneal metastases, and intrahepatic metastases for 16 patients—findings that would have precluded transplantation as well. Eleven of the 28 unresectable patients (39%) had vascular encasement precluding resection, and these patients would have been candidates for transplantation after neoadjuvant therapy.

Recently, we have administered neoadjuvant therapy to several patients found to have unresectable disease and absence of regional lymph node involvement confirmed during exploration for attempted resection. None had peritoneal exposure of tumor with transperitoneal or operative biopsy, which are known to cause tumor seeding. We have observed that subsequent transplantation is more difficult, but our limited experience precludes assessment of this approach at this time.

Twenty-three percent of our patients with underlying PSC had unsuspected tumor involvement of the common bile duct margin at the time of transplantation. Our limited experience with combined pancreatoduodenectomy has been positive: 3 of 4 patients are alive and disease-free 24 to 72 months after transplantation. We continue to check common bile duct margins at the time of transplantation and proceed with pancreatoduodenectomy if there is involvement.

The University of Nebraska developed a similar approach to the treatment of unresectable hilar CCA.[33] The Nebraska protocol employs brachytherapy at a higher dose (6000 cGy) than our protocol without external beam radiotherapy. Seventeen patients received neoadjuvant therapy and 15 underwent abdominal exploration when a donor liver became available for transplantation. Four patients had lymph node involvement or carcinomatosis and 11 underwent transplantation. Five of the 11 patients were alive and disease-free 2.8 to 14.5 years after transplantation; only 2 of the 6 deaths were due to tumor recurrence. Conceptually, the neoadjuvant protocol is similar to ours. Although there were more deaths attributable to complications of neoadjuvant therapy and transplantation, tumor response was similar to our experience.

The most serious disadvantage of the liver transplant CCA treatment protocol is the limitation of donor organ availability. Nevertheless, our results with liver transplantation and neoadjuvant therapy for patients with CCA are comparable to results of liver transplantation for patients with other chronic liver diseases and hepatocellular carcinoma at our own institution. Our results with CCA exceed national mean patient survival and warrant appropriate prioritization in deceased donor liver allocation policy. As with hepatocellular carcinoma, we will need to determine the risk for disease progression while patients are awaiting transplantation. None of our patients had progression of tumors between the staging and transplant operations, but, when donor liver allocation was largely based on waiting time, we waited with staging operations until the time neared for transplantation. During the early years of our study, nearly 40% of our patients had findings precluding transplantation. Since changes in liver allocation policy, implemented in 2003, we have proceeded with operative staging immediately after completion of brachytherapy. Very few of our patients have had positive findings. Although it is too soon to determine the risk of disease progression while awaiting transplantation, we have observed that transplantation is technically more difficult with passage of time after neoadjuvant therapy and operative staging. We are concerned that inflammation encountered at transplantation may prevent detection of disease progression and lead to an increase in disease recurrence after transplantation.

We conclude that liver transplantation with neoadjuvant therapy currently appears to have greater efficacy than resection for selected patients with localized, node-negative hilar CCA. Despite differences in the patient groups, transplantation with neoadjuvant therapy achieved better local control and higher patient survival than did conventional resection. Operative staging is essential; 23% of patients had regional lymph node metastases or extrahepatic disease which precluded subsequent transplantation. In up to 23% of patients with underlying PSC, pancreatoduodenectomy may be necessary to achieve complete extirpation of the tumor for patients with common bile duct involvement at the time of transplantation. Liver transplantation with neoadjuvant therapy should be considered as an alternative to resection for patients with hilar CCA.

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Discussions

DR. JOHN P. ROBERTS (SAN FRANCISCO, CALIFORNIA): Dr. Rosen's group has been instrumental in demonstrating that liver transplantation can help a large number of patients who have cholangiocarcinoma, and this is different from the international and national experience of cholangiocarcinoma where the outcomes have actually been very poor.

One of the issues that I think comes up and Dr. Rosen addressed in this paper is how the diagnosis of cholangiocarcinoma is made, particularly in those patients with PSC. In a previous work, many of those patients had had a diagnosis based upon the cytology, where the cytologic diagnosis based on the brush flaps is difficult and most pathologists have trouble agreeing on the diagnosis of cholangiocarcinoma versus dysplasia.

My first question has to do with the patients who didn't have PSC who underwent liver transplantation under your protocol. How many of them had a diagnosis of cholangiocarcinoma based solely on brush biopsy and how many of those patients had cholangiocarcinoma on the explanted specimen? Part of that issue has to do with those people with PSC. How many patients had brush biopsy diagnosis or cytologic diagnosis of cholangiocarcinoma who didn't have the findings at the time of explant pathology?

Given your success with the neoadjuvant therapy, do you believe that we would see better results with resection of those patients who underwent neoadjuvant therapy possibly to improve their survival after a resection or possibly the resectability?

DR. CHARLES B. ROSEN (ROCHESTER, MINNESOTA): You are correct. It is very difficult to establish a diagnosis of cholangiocarcinoma, especially in the setting of primary sclerosing cholangitis. I would like to answer your question a little bit differently by looking at our data on explanted specimens. With our transplant protocol, some of our patients did not have biopsy-proven carcinoma or cytology-proven carcinoma at the time they were entered into the protocol and

began neoadjuvant therapy. Sixteen of our 38 transplant patients did not have detectable tumor in their explanted specimens. However, 8 of those patients had unequivocal diagnoses of cholangiocarcinoma established prior to enrollment in the protocol with either transluminal cytology or biopsy. The other 8 patients did not have established tissue or cytology diagnoses, but we still felt that they had cholangiocarcinoma based on their CA-19.9 levels or ploidy studies done on endoscopically retrieved biliary aspirates. Even if we were to omit these 8 patients from our analysis, it would only change the 5-year survival from 82% to 80% - so we chose to keep them in. Also, 3 of the 14 patients that were positively staged did not have cytological or histological confirmation of cholangiocarcinoma prior to enrollment in the protocol, and obviously these 3 patients had tumor.

Your question about resection with neoadjuvant therapy is very appropriate, and it is a question that we are often asked. One needs to really appreciate the changes that occur in the hilus of the liver as a result of the neoadjuvant therapy, and I think that a subsequent nontransplant operation would be fairly difficult.

We have largely abandoned use of the common hepatic artery for reconstruction with deceased donor livers. Often, it is difficult enough just to oversew it, let alone use it for an anastomosis. The tissues can be quite friable as a result of the neoadjuvant therapy. The portal vein can also be very brittle. One of the disease-specific problems we have encountered after transplantation has been portal vein stenosis, which is a very rare complication after liver transplantation for other diseases without without neoadjuvant therapy.

Dr. Roger L. Jenkins (Burlington, Massachusetts): In the early days of liver transplantation it was natural to assume that this was the best modality of treatment since the tumor often invades into the portal vein or the hepatic artery, and one way of removing all of the surrounding tumor would be to perform a transplant. Of course the results were miserable in those days and most of us stopped doing liver transplants for hilar cholangiocarcinoma.

Many surgical techniques have been developed to further our ability to achieve negative margins, including major lobar resection, caudate lobe resection and resection of vascular structures with reconstruction. Even with all of those improvements in surgical technique, we have never really achieved survival rates that exceed 40%. So your results are an important finding and have been consistent as time has gone on.

I have a number of questions for you, however, relating to the implementation of the actual program. Live donor liver transplantation has been used relatively sparingly in your population; I think rightfully so. Nowadays, patients oftentimes come to us with a new diagnosis of a bile duct cancer bringing a donor in tow and asking us to consider transplantation.

Obviously, the MELD system has had an impact on your ability to provide cadaveric organs for this patient population. Are these patients sick enough to be able to be transplanted based upon their MELD scores, or are you doing this as a regional variance where you have to get buy-in from other programs? I think that is a very important concept because you may be the only program regionally performing this procedure for bile duct cancers and the buy-in of the other programs is essential.

What have you done with immunosuppression? Have you done anything specific for these tumor patients in terms of avoidance of steroids or other things that we try in our hepatocellular carcinoma population?

I am very curious as to how patients enter into the system. Are they referred to the hepatobiliary surgeon or the transplant team? How does the transplant team and the hepatobiliary team interface? How do you decide whether or not a patient is actually resectable, whether they should be considered for attempts at resection?

Most importantly, however, how are you educating your nonsclerosing cholangitis patients about what the best treatment modality is? You have wonderful results with transplantation but results that are fairly typical of what we all get with non-transplant resection at this point. What do you tell your patients? Should they all be considered for resection or should they all be entered into the transplant protocol?

Dr. Charles B. Rosen (Rochester, Minnesota): As you well know, we started doing living donor liver transplantation for these patients several years ago. I originally thought that it would be an excellent application for the procedure. We did 4, and our results were somewhat miserable. We abandoned it for a year or 2 and then resumed living donor liver transplantation during this last year. There were a total of 7 in the series that I presented today. Currently, approximately half of our living donor liver transplants done at Mayo Clinic Rochester are for hilar cholangiocarcinoma.

I think the mistake that we made with the first 4 patients was that we were expanding our inclusion criteria at the same time we introduced living donor liver transplantation. One of the first 4 patients had a Whipple procedure. Another had a Wall stent that leaked and eventually led to the patient's death.

Our early living donor experience with noncholangiocarcinoma patients was excellent. Now use living donor liver transplantation for those patients that we anticipate will have fairly straightforward operations, and our results are good. During 2004 our results with living donors have actually been better from a morbidity standpoint than our results with deceased donor transplantation. The living donor recipients

avoid the prolonged waiting time between staging after neoadjuvant therapy and transplantation.

We have had difficulty with deceased donor liver allocation. The deceased donor organ shortage is obviously the biggest difficulty with liver transplantation overall. Fortunately, in our region we have been able to work out an agreement with our colleagues, especially those at the University of Minnesota – the only other liver program in our organ procurement organization. Thanks to Bill Payne and Jack Lake at the University of Minnesota, we reached an agreement regarding allocation of deceased donor livers for patients with cholangiocarcinoma. They have both recognized the efficacy of the treatment protocol. We agreed to an appealed MELD score of 20 for patients after negative staging operations. The appealed scores are then increased in an increment equivalent to a 10% increase in mortality at 6-month intervals (rather than the 3-month intervals for patients with hepatocellular carcinoma).

We have also used a number of expanded criteria donors, and approximately half of the donors for our cholangiocarcinoma patients are either living donors or expanded criteria deceased donors. Just the other day, we used an 82-year-old donor liver for a patient with cholangiocarcinoma.

We have had several patients with sclerosing cholangitis decompensate after staging or during neoadjuvant therapy. Several of those patients have received deceased donor livers on the basis of their calculated MELD scores.

Your second question pertained to immunosuppression. We have not changed our immunosuppression protocol after transplantation for the cholangiocarcinoma patients. They generally receive a calcineurin inhibitor, mycophenolate mofetil, and steroids – withdrawing the latter two within the first six months after transplantation.

You asked how patients enter our system, and it is variable. Some patients come to us after learning about our protocol on the internet and contacting Dr. Gores or myself. Others are referred to us from surgeons, oncologists, hepatologists or our colleagues at the Mayo Clinic.

Fortunately, our decision-making process has been fairly straightforward. Those patients that have had disease that appeared unresectable to an experienced hepatobiliary surgeon and those patients with disease in the setting of sclerosing cholangitis are generally treated per the liver transplant protocol. Those patients who have had tumors that appeared amenable to resection have generally been treated with an operation intended to achieve potentially curative resection. Patient counseling is in line with our institutional approach to this disease.

Dr. Byers W. Shaw, Jr. (Omaha, Nebraska): There are some things that you emphasize in the manuscript that are probably worth talking about briefly.

As you know, we got interested in trying to change the results of transplantation for cholangiocarcinoma, as you mentioned, in the late 80s, and we were grateful that the Mayo Clinic sent us quite a few of our initial patients. Our results in about the first 5 or 6 patients were encouraging, as you mentioned. And even our failures were proof that perhaps our concept was right.

Our concept was that we were interested in preventing what at the time appeared to be the most common pattern of recurrence after liver transplant for cholangiocarcinoma, namely either the peritoneal seeding or local recurrence. Our thinking was that we were probably spreading tumor around at the time of transplant, or many times the tumor had already been spread by prior surgical efforts at resection that were incomplete, or even by prior biopsies. There were some fairly interesting anecdotal experiences that I had in Pittsburgh that served as the basis for trying to do something. These were a relatively small group of patients, as you emphasize in your manuscript. The selection here is probably limited to a small group of patients.

But I am encouraged that your results have held up and am jealous of the numbers of patients you have been able to accumulate. We certainly found ourselves unable to treat these patients in the late 1990s and early 2000s once organ availability became much less. It was not until living donation became more available that we were able to start doing some of these cases again. One wonders whether results like you have shown may actually result in the need to give some extra MELD points to some of these patients. I would like you to comment on that. I have two specific questions.

One of them is: In your R-0 resection patients, what was the specific pattern of recurrence in those patients and does it suggest, as John Roberts already hinted, that perhaps these patients would have benefited? For instance, if this is largely local recurrence, as some of them appear to be, at least in the overall recurrence after resection, are the R-0 patients the ones that may have benefited from a preoperative approach?

The second question is: You didn't mention whether or not you have had PSC patients that on explant were found to have cholangiocarcinoma that you didn't know they had. We have certainly seen a fair number of those patients over the years, and the results in those patients are almost universally dismal with very high recurrence rates and ultimate death from recurrence.

Finally, you mentioned that our dose of radiation in your manuscript was higher than yours. And I think that that has been a mistake on our part to use higher doses. That was something that actually started more recently and was not part of our initial protocol and I think the radiotherapists began to get enthusiastic that they could cure more cancer by giving more radiation. I think the few examples you have of some damage to the vessels in the hilum has been our experience as

well, and we have gone to even using lower doses of radiation than even what you are currently recommending.

DR. CHARLES B. ROSEN (ROCHESTER, MINNESOTA): Thank you, Dr. Shaw. I really appreciate your comments as well as the help that you have given to our program over the years in establishing this protocol.

Recurrences are a key issue to understanding our results. Although we have only seen 5 recurrences in our transplant patients, they tend to be distant, osseous, for example. In contrast, the recurrences that we have seen in our resection patients were largely local. Thus, we think that neoadjuvant therapy and the wider excision achieved with transplantation are indeed obtaining better local control of the disease.

Fortunately, our experience at Mayo with the detection of incidental tumors in patients with PSC has been fairly modest. Early on, we transplanted 54 patients with PSC before we found an incidental tumor and that patient - contrary to most everyone else's experience – actually lived for 10 years before dying from cardiovascular disease. As we know, in your experience, as well as those reported in the tumor registry and Canadian and Spanish experiences, the outcome for patients with incidental tumors has been dismal. We do everything that we can to rule-out cholangiocarcinoma prior to transplantation for PSC patients. Hopefully, some of the new cytological techniques, those that detect aneuploidy, may help us avoid the mistake of a missed tumor.

Your question about MELD scores clearly warrants discussion. One of the difficulties we have is that we don't know where to start. We arbitrarily made a decision to start at 20 in Region 7 since that is where we were starting at that time with small hepatocellular carcinoma. We also don't know how quickly and with what increments the patients should have increases in their scores. To answer these questions, we will need to know the rate of disease progression with neoadjuvant therapy and the risk for disease progression beyond transplant criteria.

In the early years of our experience, we performed the staging operation as the time neared for transplantation. As a result, none of our patients were observed to have disease progression. Now we perform the staging operation earlier - immediately after neoadjuvant therapy - and we may have more patients with disease progression at the time of transplantation. We and our colleagues at the University of Minnesota realized these concerns when we agreed on organ allocation within Region 7. My concern, however, is that the change in the timing of the staging operation - along with the progressive increase in difficulty with the transplant operation as patients await transplantation - may result in our missing tumor progression. We may end up with more recurrences after transplantation. It is also more difficult to do the transplants the longer patients wait after neoadjuvant therapy and staging.

DR. JEAN C. EMOND (NEW YORK, NEW YORK): I wanted to ask you about the living donors. The grafts come with no vessels. Have you been adding interposition grafts from either the donor or third party so that you can do a real cancer operation in a recipient, and is that an issue? A related question is: Have you thought about just sending these people to Mayo-Jacksonville where there are so many donor livers since it is your sister program?

DR. CHARLES B. ROSEN (ROCHESTER, MINNESOTA): Our colleagues at Mayo Clinic Jacksonville have a protocol in place as well, but there are some minor differences in administration of neoadjuvant therapy.

We use deceased donor vessels with living donor liver transplantation. Reconstruction of the portal vein requires an interposition graft between the donor right portal vein and the recipient portal vein. We often use an iliac artery from the same deceased donor for arterial reconstruction. More recently, if the recipient artery appears healthy, we may perform an anastomosis directly to the recipient artery.

We are aware of the good tissue practices that are being put in place by the government. We intend to do everything possible to comply with them, but we clearly have a need for deceased donor vessels in order to transplant patients with living donor livers.

DR. WILLIAM J. WALL (LONDON, ONTARIO, CANADA): Cure of cancer is the objective of your treatment. Certainly you accomplished that in your transplant group, and the results are spectacularly good.

You indicated that the cancer recurrence rates in the resected group were only about 30%, and yet the 5-year survival was as low as 20% in the resected group. One wonders if there were some noncancer causes of death in that particular group that helped to explain the difference in survival at 5 years.

You indicated that the resected group were older than the transplanted group. Was there substantial mortality that was not cancer related that helped to contribute to the difference in survival?

DR. CHARLES B. ROSEN (ROCHESTER, MINNESOTA): There were 3 postoperative deaths in that group. Those deaths, along with the recurrences and subsequent deaths due to cancer, account for the survival results for those patients. There are age differences between the groups, and it is difficult to correct for that. Removing the sclerosing cholangitis partly corrects for the age difference, but clearly, patients that undergo resection are older than those that undergo transplantation - or at least they have been up until the present time.